

## Hypercalcemia and Carcinoma of the Penis

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Hypercalcemia is the most common metabolic disorder associated with malignancies. Squamous cell carcinoma of the penis is a tumor for which this abnormality has rarely been described. This report presents a case of hypercalcemia seen in a patient with advanced penile cancer. A chemotherapy regimen of

intravenous cisplatin and fluorouracil caused regression of the primary tumor and normalization of the serum calcium. A literature review supported an association between squamous cell carcinoma of the penis and hypercalcemia. *Med. Pediatr. Oncol.* 29:576–577, 1997.

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**Key words:** hypercalcemia; carcinoma of the penis; chemotherapy

### INTRODUCTION

Hypercalcemia is the most common life-threatening metabolic disorder associated with malignancies [1,2] and is identified in certain genitourinary malignancies, such as carcinoma of the kidney [3]. It has rarely been reported in association with primary squamous cell carcinoma of the penis [4]. Ideally, treatment of the primary cancer leads to resolution of this paraneoplastic disorder; however, elevated calcium levels often necessitate urgent, non-specific measures, including hyperhydration therapy, diuretics, and bisphosphonates [3]. We describe a case of hypercalcemia seen in a patient with advanced squamous cell carcinoma of the penis and report on the management of the primary cancer and the serum calcium abnormality. The literature was reviewed to determine whether an association between hypercalcemia and cancer of the penis has been observed.

### Case Report

A 53-year old Caucasian male was referred with a three month history of a progressively increasing painful mass in the left groin. A right groin mass had been noted a few weeks before and was biopsied showing infiltrating moderately differentiated keratinizing squamous cell carcinoma. Constitutional and hypercalcemic symptoms were absent.

At examination the patient was uncircumcised and had bilateral inguinal lymph node enlargement with a necrotic ulcer on the left side. Left femoral nodes were also enlarged and the left leg was edematous. An indurated firm lesion of the glans penis made retraction of the foreskin difficult. Laboratory investigations revealed serum calcium to be elevated at 3.25 mmol/L (normal range 2.12–2.62 mmol/L) with serum albumin decreased at 33 g/L (normal range 35–50 g/L) and normal renal

function tests. Serum parathormone and parathormone-related (PTH-rp) levels were not done.

There was no evidence for bone metastases. Chest radiograph revealed left lung nodular densities suggestive of metastatic disease. Biopsy of the penile lesion revealed infiltrating moderately differentiated keratinizing squamous cell carcinoma. A diagnosis of metastatic carcinoma of the penis with concurrent hypercalcemia was made.

The patient was admitted to hospital and treated with large volume intravenous normal saline. No bisphosphonate was given. Subsequently, the patient received an intravenous chemotherapy with cisplatin (100 mg/m<sup>2</sup> day 1) and fluorouracil (1000 mg/m<sup>2</sup>, days 1–5). The patient's serum calcium normalized with the first cycle. Two further cycles were subsequently given. The inguinal lesions decreased in size and serum calcium level remained normal.

Thereafter, the patient declined further chemotherapy and failed to return to clinic for scheduled follow-up. He returned three months later with newly enlarged nodes especially in the left groin and a small amount of penile edema. Chest radiograph revealed an enlarged left lung nodule. Serum calcium was measured at 3.04 mmol/L with a serum albumin of 32 g/L. Further chemotherapy was declined and palliative radiotherapy was given to the inguinal and pelvic nodes and penis. Treatment consisted of 2200 cGy in 5 fractions delivered by parallel opposed antero-posterior fields on the Cobalt unit. While receiv-

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Received 23 October 1996; Accepted 28 April 1997

ing radiotherapy, the patient was admitted to hospital in order to treat his hypercalcemia. Initially intravenous hydration and diuretic were given, then he was treated with intravenous etidronate (7.5 mg per kg daily for five days). Serum calcium was normal at discharge and he was discharged on oral etidronate (400 mg twice daily). Thereafter the patient was not seen in follow-up. He died four months later.

### Comments

In North America, carcinoma of the penis is a rare neoplasm representing less than 1% of all cancers in males [4]. A survey of the scientific literature from the past 15 years revealed three descriptions of hypercalcemia in conjunction with primary cancer of the penis. In the case reported by Glenn [3], a patient with stage II (AJCC classification) squamous cell carcinoma of the penis was found to be hypercalcemic on presentation. Definitive management of the malignancy consisted of a subtotal penectomy. The author reported that the serum calcium abnormality began to resolve within 24 hours of the surgery and normalized over the next month.

Dexeus and his colleagues [5] examined the response of 14 patients with recurrent or inoperable carcinoma of the male genital tract to a combination chemotherapy regimen consisting of methotrexate, bleomycin and cisplatin. Two of the 12 patients with advanced carcinoma of the penis were hypercalcemic. Significant clinical responses to the chemotherapy were reported in 10 of the cases under investigation and these included both patients with hypercalcemia. Additionally, the authors noted that the hypercalcemia in these two men resolved with the chemotherapy regimen.

The present report describes a patient treated with chemotherapy known to be active in penile carcinoma [6,7] which resulted in clinical partial response. Interestingly, a rapid normalization of serum calcium levels was also achieved concurrent with response to treatment. When the patient elected to discontinue treatment, tumor recurred rapidly. Hypercalcemia recurred simultaneously strongly suggesting this was due to a paraneoplastic effect. Unfortunately, PTH-rp levels were not drawn to confirm definitively this association.

The reports of Dexeus [5] and Glenn [3] as well as this case report demonstrate correction of hypercalcemia concurrent with response to chemotherapy in penile carcinoma. Glenn's case report [3] is particularly interesting in its description of hypercalcemia in early stage disease, suggesting humoral hypercalcemia of malignancy as seen in other squamous cell cancers and associated with production of PTH-rp [8]. The absence of PTH-rp data in our case does preclude any definitive statements on a causal link between hypercalcemia and the primary malignancy. However, these consistent observations of normalization of serum calcium levels concurrent with tumour response to chemotherapy are highly suggestive of a paraneoplastic basis for this metabolic abnormality. In future, this could be confirmed by PTH-rp measurements.

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